UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 15, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

DATE: June 17, 1998

MEMORANDUM

SUBJECT: Methidathion: Rebuttal on Toxicology Endpoint Selection

FROM: Yung G. Yang, Ph.D.
Toxicology Branch 1
Health Effects Division (7509C)

THRU: Alberto Protzel, Ph.D.
Branch Senior Scientist
Toxicology Branch 1, HED (7509C)

TO: Kathy Monk / Michael Goodis
PM 52
Reregistration Division (7508W)

DP Barcode: D244128
Case: 815719
Submission: S538337
ID No.: 100301-000100
Chemical: Methidathion
PC No.: 100301
Registrant: Novartis Crop Protection, Inc.

ACTION REQUESTED: Review a rebuttal from the Registrant concerning Toxicology Endpoint Selection for Methidathion.

BACKGROUND: On June 4, 1996 the HED Toxicology Endpoint Selection Committee evaluated the available toxicology data for Methidathion, identified toxicology endpoints and selected dose levels for risk assessments on acute dietary as well as occupational or residential exposures. The Registrant did not agree with the Agency's decision and submitted a rebuttal (dated February 16, 1998) addressing its concern and proposed endpoints and doses for the acute, short term, intermediate, and long term exposure.

RESPONSE: The Health Effect Division's Hazard Identification Assessment Review Committee (HIARC) conducted a comprehensive

review of the organophosphates including Methidathion on May 1998. The HIARC's assessment entailed reviewing consistency of the decisions made previously by the Committee with regard to the assessment of neurotoxicity, the determination of enhanced susceptibility for infants and children from exposure to these chemicals as required by the Food Quality Protection Act (FQPA) of 1996, the recommendations on the FQPA Safety Factor, and the toxicological endpoints selected for acute and chronic dietary as well as occupational or residential exposure risk assessments. The Committee's conclusions on endpoints and dose selection for Methidathion are presented below.

Endpoints & Doses Selected for Dietary & Non-Dietary Exposure Risk Assessment on Methidathion

Acute Dietary NOEL (mg/kg)	Chronic Dietary NOEL (mg/kg/day)	Dermal Absorption Factor	Dermal Exposure			Inhalation Exposure (any time period) NOEL (mg/L)
			Short-Term	Intermediate-Term	Long-Term	
			NOEL (mg/kg/day)			
0.2	0.15	100%	0.2	0.2	0.15	Oral equivalents
90-Day Rat: ↓ Plasma, RBC & Brain ChE	1-Year Dog: ↓ RBC ChE; Liver lesions	(Default)	90-Day Rat: ↓ Plasma, RBC & Brain ChE	90-Day Rat: ↓ Plasma, RBC & Brain ChE	1-Year Dog: ↓ RBC ChE; Liver lesions	Oral Studies/ endpoints used for dermal exposure

Data extracted from attachments #4&5 of the memorandum (Organophosphates: A comprehensive review for FQPA) from J. Rowland to L. Rossi, dated June 3, 1998.

Detailed responses are as follows.

1. <u>Acute Dietary</u>

The Registrant proposed a dose level of 1 mg/kg from an acute neurotoxicity study in rats (MRID# 44434501) for use in acute dietary risk assessment. The Registrant stated that “although AChE inhibition in the cerebral cortex was observed in males at 1 mg/kg, this finding is considered spurious and of little toxicological significance based on the following observations: Inhibition in RBC has consistently been demonstrated to be the most sensitive indicator of cholinergic toxicity in acute and subchronic toxicity studies with Methidathion.” However, the Agency’s review indicated that “although these decreases in brain cholinesterase were not associated with clinical signs or gross

or microscopic pathology, they are still believed to be of toxicological significance due to the magnitude of depression (↓41%) occurring after a single dose and the observations made at subsequent dose levels. At higher doses of Methidathion, there was a greater depression and a correlation between the observed depression and clinical manifestations. This implies that the findings at 1 mg/kg are real, are treatment related and should be considered biologically significant." (Memorandum, M. S. Morrow to L. Schnaubelt, dated June 21, 1994).

The Registrant also mentioned a human study (MRID# 0011820). In this study, eight men received daily oral capsules containing 0.11 mg/kg Methidathion for 42 days. There were no indications of plasma or RBC ChE inhibition, no changes in cardiac function, hematology, serum chemistry, physical parameters or urinary data. However, the Agency's toxicology database showed that this mentioned human study was a summary report. Until the complete study is submitted and accepted by the Agency, this study cannot be used for endpoint or dose selection. Results given in a summary report often do not agree with the same entries in the detailed report.

2. Chronic Dietary

The Registrant concurred with the Agency's selections.

3. Short- and Intermediate-Term Dermal Exposure

The Registrant proposed an endpoint of 5 mg/kg/day, based on observed clinical signs of toxicity at 20 mg/kg/day, from a 21-day dermal toxicity study (MRID# 40079804). Another 21-day dermal toxicity study in rabbits (MRID#40079806), used to support the Agency's choice of critical study, showed that the NOEL was less than 1 mg/kg/day based on mortality and clinical signs (anorexia, ataxia, bloated, hunched, languid, altered respiration and soft feces) consistent with ChE inhibition at 1 mg/kg/day in males. The Registrant stated that these toxicity results were compromised by the high degree of stress to the animals caused by the study conditions. The Agency's review, however, indicated that mortalities were observed in the males at all treatment levels and in the females starting from 10 mg/kg/day. Since there were no deaths in the control group and other evidence of toxicity was present at the lowest dose tested, these deaths may have been treatment-related. Although the study was classified as supplementary, it can be upgraded based on criteria developed during the rejection rate analysis which stated that the lack of a NOEL and the use of an occlusive bandage would not be sufficient reasons to reject a dermal toxicity study.